Dec. 5, 1950 G. V. TAPLIN ET AL 2,533,065

MICROPULVERIZED THERAPEUTIC AGENTS

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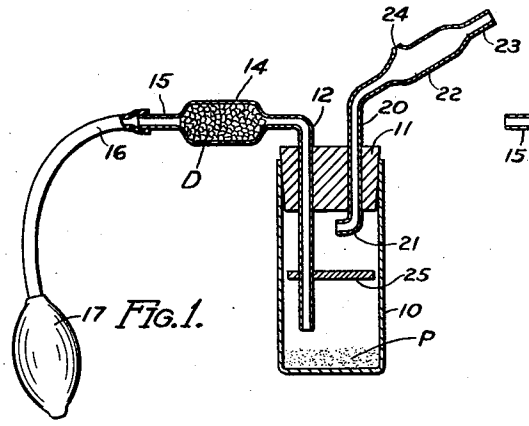


FIG. 1.

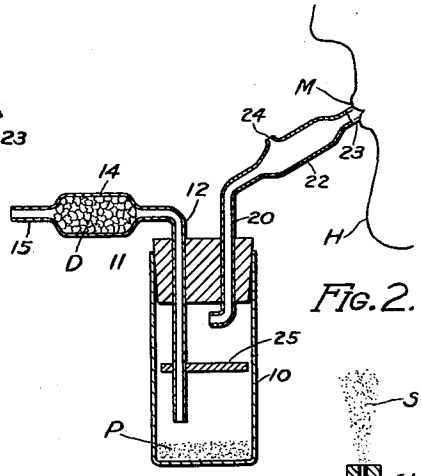


FIG. 2.

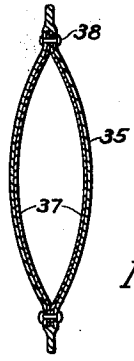


FIG. 5.

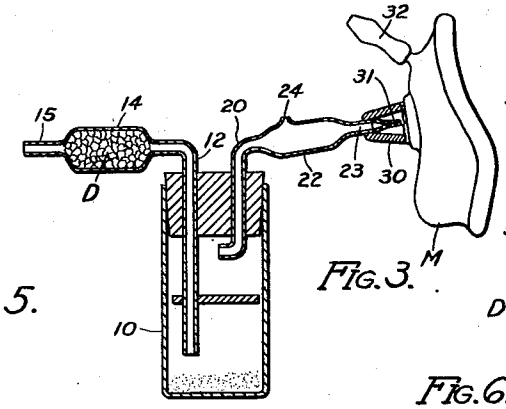


FIG. 3.

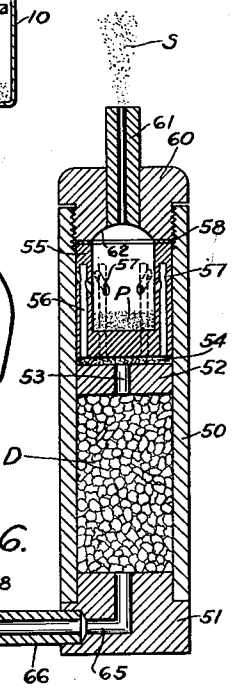


FIG. 6.

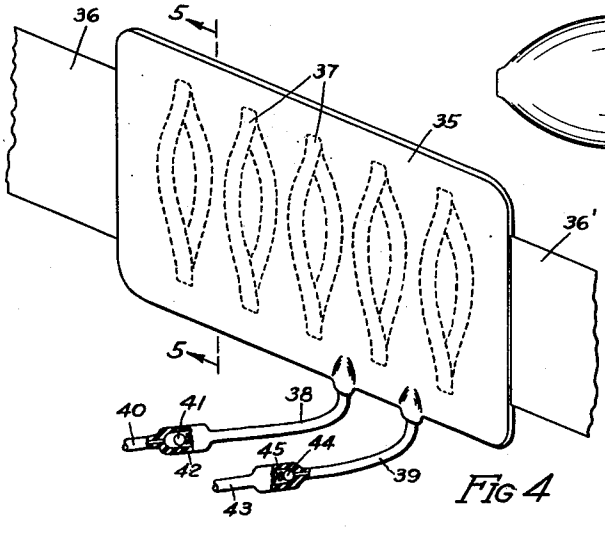


FIG 4

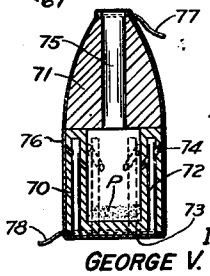


FIG. 7.

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MICROPULVERIZED THERAPEUTIC AGENTS

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Application March 8, 1947, Serial No. 733,280

5 Claims. (Cl. 167—65)

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The present invention relates to therapeutic agents and to a method for administering the same. In particular, the invention relates to absorbable therapeutic agents which can be produced in powdered form.

The invention is applicable to the preparation and administration of any absorbable therapeutic agent, such as, for instance, penicillin, streptomycin, any of the sulfonamides, adrenalin, "Tuamine," "Neosynephrine," etc., whether used singly or in combination. For the purpose of an understanding the invention, however, it will be described specifically first in connection with the preparation and administration of penicillin. The wide variety of uses, to which the invention may be put will be pointed out more in detail hereinafter.

Heretofore, one common way of administering penicillin has been by nebulizing a penicillin solution and inhaling the spray or vapor so produced. This method of administering penicillin, which is known as the aerosol principle, has, however, many disadvantages.

To produce the spray, air must be pumped manually through an atomizer or nebulizer containing the pencillin solution, or a tank of oxygen must be connected to the atomizer or nebulizer. While tanks of oxygen are relatively easy to procure in a hospital, they are hard to get for use in the home. Moreover, they are an expensive means for producing the pressure sufficient to form a spray. They add materially, also, to the weight and cumbersomeness of the nebulizer. Hand pumping, on the other hand, is a long, tedious operation. It may take one-quarter to three-quarters of an hour to administer a treatment of the required number of units of penicillin with a manually operated spray. Even with the oxygen tank, it takes 15 to 20 minutes to administer the required dosage. The length of time required to administer a dose is very tiring to the patient and often the irritation and nervous tension to which the patient is subjected during the long period required for administering the drug offsets to a large extent the beneficial effects of the dosage.

Furthermore, the aerosol method of administration is inefficient and wasteful. For a treatment of twenty-five thousand to fifty thousand units of penicillin, fifty thousand to one hundred thousand units may have to be employed; so much of the penicillin is dissipated and lost in the air in the spray. In order that the patient may obtain the required number of units of penicillin in a day, then, four or five doses per day may have to be administered.

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A further drawback of the aerosol method of administration is the instability of penicillin in solution. Penicillin solutions deteriorate rapidly, and must be kept refrigerated to retain their full potency for even a week.

One object of the present invention is to provide a new form in which therapeutic agents, such as penicillin, can be produced, to enable such substances to be administered much more rapidly and much more efficiently than heretofore.

Another object of the invention is to provide a form in which therapeutic agents may be administered, which will be stable and which can with ease be so preserved as to retain more or less indefinitely the potency of the agent.

Another object of the invention is to provide a simple method for administering therapeutic substances whereby the required dosage can be supplied in an extremely short period of time, and effortlessly so far as the patient is concerned.

A further object of the invention is to provide simple, inexpensive apparatus for administering therapeutic agents in powdered form.

Still another object of the invention is to provide a piece of apparatus for administering therapeutic substances, which will be light in weight and of a size that can readily be carried around in the pocket of a patient.

A still further object of the invention is to provide a piece of apparatus for administering therapeutic substances, which is simple in construction, quite inexpensive, and which can readily be operated by the patient himself without effort.

Other objects of the invention will be apparent hereinafter from the specification and from the recital of the appended claims.

It is well known that penicillin can be produced in crystalline form, but heretofore the crystals of penicillin have been dissolved in a saline solution and the penicillin administered, as already described, in the form of a vapor. The present invention is based on the use of penicillin and other soluble therapeutic agents in the form of powder, and upon the administration of the agent by particulate suspension of the agent in air, so that a powder smoke is produced, which can be inhaled or applied topically. The powdered penicillin can be obtained by grinding crystalline penicillin in a ball-mill or other suitable apparatus to a powder with a particulate size of less than one micron. Thus the powder particles are of the approximate size or may be even smaller than the size of the droplets produced by a nebulizer.

It has been found that when micro-pulverized penicillin is administered by particulate suspension in air, a dose of twenty-five thousand to fifty thousand units of penicillin can be administered in one or two minutes or less. Moreover, the powdered penicillin can easily be carried in an air stream produced by simple inhalation through the mouth or by pressure on an ordinary rubber air bulb. The administration of the penicillin or other therapeutic agent in the novel form of the present invention can be effected therefore without effort; and there is no need for the use of oxygen or any other mechanical source of pressure. It has been found, too, that when penicillin is administered in this way, the efficiency of the dosage is 93 to 95 per cent, so that the cost and the number of dosages are reduced very considerably from those heretofore required.

Moreover, since there are seventy square meters of surface in the lungs, the very fine particles of penicillin supplied to the lungs by the present method are absorbed quickly and over so great an area that a dosage of penicillin administered according to the present invention is extremely effective, so that the disease, for which the dosage of penicillin is prescribed, can be brought under control much more quickly than by previous methods of administration. Aside from the local action of the penicillin on the lungs, it is picked up quickly by the blood stream.

Because of the high potency of pure penicillin, it has been found desirable in practice to mix the penicillin with anhydrous glucose or a similar vehicle in the proportion of 1 : 5 to 1 : 20 and to grind the mixture together to a powder. This mixture provides an inexpensive, but effective therapeutic agent, and when inhaled in the form of a smoke produces practically no bronchial irritation, while the taste is a mixed one of faint bitterness and sweetness. Because of its glucose content, moreover, the mixture is additionally beneficial to a patient.

In the apparatus for administering the powdered penicillin, it is desirable to provide two chambers, which are connected together. In the first of these chambers, which is that through which the air passes first, there is provided some substance which will absorb the moisture out of the air, so that the air will be dry when it passes into the second chamber, which contains the penicillin powder. This moisture absorbing substance may be anhydrous calcium sulfate or a similar substance, and this may be mixed with a litmus-type indicator which will show by change of color when the dehydrating material has picked up all of the moisture it can hold. Various such materials are well known and are sold extensively under different trade-names.

It is also within the contemplation of the invention, however, to use a disposable container containing a single specific dose of the therapeutic agent. This container, which may be made of papier-mâché, is provided with inlet ducts through which air is admitted to the powder chamber and an outlet duct through which the powder in suspension may be inhaled through the nose or mouth. The container is intended to be sold with the dose in it and with the dose protected against moisture by an air-tight covering which encloses the whole container. This covering is ripped away when the dose is to be used, and the container is intended to be thrown away after use.

In the drawings:

Fig. 1 is a sectional view of a piece of apparatus built according to one embodiment of this invention for administering a therapeutic agent, and having an air bulb for producing the air stream that picks up the therapeutic powder;

Fig. 2 is a sectional view of the apparatus shown in Fig. 1, but illustrating how, by removal of the air bulb, the apparatus may be employed for inhaling the therapeutic substance through the mouth;

Fig. 3 is a sectional view, showing how the apparatus of Figs. 1 and 2 may be adapted for use with a face mask;

Fig. 4 is a perspective view showing a pressure cuff such as may be employed around the chest of a patient in a weak, or comatose condition, to produce the air stream;

Fig. 5 is a section on the line 5—5 of Fig. 4;

Fig. 6 is a sectional view of a piece of apparatus built according to the present preferred embodiment of this invention; and

Fig. 7 is a sectional view of a disposable combined container and inhaler made according to one embodiment of this invention.

Fig. 1 shows a very simple form of apparatus constructed according to this invention for administering a powdered therapeutic agent. Here, 10 denotes a container that may be made of glass or of a suitable plastic. The open end of this container is closed by a rubber stopper 11. This stopper has two holes in it. Through one of these holes there passes a tube 12, which extends downwardly a considerable distance into the container. This tube is formed exteriorly of the container with an enlarged portion forming a chamber 14, and beyond this chamber the tube terminates in a reduced end portion 15. The tubular end 16 of a suitable rubber air pressure bulb 17 may be connected to the end 15 of the tube as shown in Fig. 1. Through the other hole in the stopper 11, there passes a tube 20, which has its end turned at an angle below the stopper 11, as denoted at 21. Exteriorly of the container, this tube 20 is formed with an enlarged portion 22, and it terminates in a reduced end portion 23. The enlarged portion 22 of the tube 20 has an opening 24 formed in one side thereof, to provide an air vent. The tubes 12 and 20 may be made of glass, or of plastic, or of a suitable metal, such as copper.

The therapeutic agent, which is to be used, which may be, for instance, finely powdered penicillin, whose particulate size is one micron or less, or which may be powdered penicillin mixed with powdered glucose or starch in the form of a micropulverized powder, is placed in the container 10, being denoted at P. A suitable dehydrating substance, such as anhydrous calcium sulfate, denoted at D, is placed in the chamber 14 of tube 12. This preferably is employed in the commercial form in which it is mixed with a litmus agent so that it will turn from blue to pink, when it has picked up all the moisture which it can.

In use, if a person wants to administer the penicillin, or other therapeutic agent to a patient, or if the patient wishes to administer it to himself, the end 23 of tube 20 may be placed in one nostril of the patient, and the bulb 17 is alternately squeezed and released. Thus, a stream of air, is forced through the dehydrating substance D, down through the tube 12 into the container 10. The pressure of this air, forces the powder P in the container up through the

tube 20 and out through the end 23 of this tube in a form like smoke; and the patient inhales this therapeutic smoke.

A baffle 25 is secured in any suitable manner to the tube 12 some distance above the lower end thereof, so as to prevent the powder P from being expelled from the container in lumps or gobs. These might irritate the throat, and would be wasteful of the medicine. The baffle is circular and there is but a slight difference between the diameter of the baffle and the internal diameter of the container, so that the only way in which the particles of powdered penicillin can reach the tube 20 is around the periphery of the baffle.

The vent 24 in the tube 20 admits of an additional current of air being drawn into the tube 20 as the stream of powder and air passes through that tube. This additional air stream serves to keep the powder stirred up and agitated and further insures that it will pass out of the end 23 of the tube 20 in the desired form of smoke. If the vent were not provided, too much powder might be expelled from the end 23 of the tube at one time; and this would be wasteful.

The same piece of apparatus shown in Fig. 1 can be used without change for inhaling the penicillin, or other therapeutic agent, through the mouth. Thus, after removing the tube 16 and air pressure bulb 17, the patient, part of whose head is denoted at H in Fig. 2, can place the end 23 of the tube 20 in his mouth M and suck air through the end 15 of the tube 12, through the dehydrating substance D, into the container 10, and thence draw the powder suspended in air through the tube 20 into his mouth. In this case, an additional current of air is usually not required, and the patient can close the vent 24 with his thumb.

The same piece of apparatus can be used, also, without substantial change, in connection with a face mask where it is desirable to employ such a mask in the administration of a therapeutic substance to a patient. In this case, the end 23 of tube 20 is inserted into an opening formed on the projecting portion 30 of the face mask M (Fig. 3), and there is a rubber flap valve 31 applied over the end 23 of tube 20. The face mask itself, which is shaped to fit the contour of the face, has a further rubber flap valve 32 secured to it at any suitable point. The rubber flap valve 31 permits of the powdered penicillin and air being drawn into the face mask as the patient inhales. It closes when the patient exhales. The rubber flap valve 32 allows of the air being exhausted from the mask when the patient exhales.

When a patient is in a weak or comatose condition, or lacks the power of coordination, the air pressure for forcing the powder out of the container may be supplied by the movement of the patient's chest as he alternately inhales and exhales. Thus, a pressure cuff, such as denoted at 35 in Fig. 4, may be fastened around the chest of the patient by webbed straps 36 and 36'. These straps are secured to opposite ends of the pressure cuff and may be fastened together at their free ends by a buckle or any other suitable fastening means. This pressure cuff has a plurality of flat, generally elliptical form springs 37 fastened therein by any suitable means, such as rivets 38. There are two tubes 38 and 39 connected with the pressure cuff. The tube 38 is open to the air at its end 40, and it has a ball valve 41 mounted therein which is normally pressed to closed position by a coil spring 42. The tube 39 is adapted to have its end 43 connected to the end 15 of the tube 12 of the apparatus shown in Fig. 1, in place of the tube 16 and air pressure bulb 17. This tube 39 has a ball check valve 44 mounted therein, which is adapted to be pressed to closed position by a coil spring 45.

The pressure cuff is adapted to be secured to the patient when the patient's chest is fully expanded, that is, at full inspiration, and when the springs 37 are fully collapsed by the pressure of the patient's chest on the pressure cuff. As the patient exhales, the springs expand, and the valve 41 opens, allowing the bag 35 to fill with air. When the patient inhales, the chest expands; the valve 41 is closed; and the air is forced out of the bag 35 through the valve 44, which is opened by the pressure of this air, and into the end 15 of tube 12. Thus, the movement of the patient's chest will operate the apparatus of this invention and supply him with the therapeutic agent in the form of smoke so that he can inhale it into his lungs. A nose clip may be necessary to secure the end 23 of the tube 20 in position so that the patient can breathe the smoke in through his nose.

The present preferred form of apparatus for dispensing therapeutic substances according to the invention is disclosed in Fig. 6. This comprises a tube 50 made of glass or plastic, one end of which is closed by a bottom cap piece 51. If the tube 50 is made of plastic, this cap piece may be made of plastic, also, and it may be secured in the tube 50 simply by friction. Secured in the tube 50 by friction or in any other suitable manner, about midway of the height of the tube is a partition member 52. This divides the tube 50 into a lower and an upper chamber. The lower chamber is adapted to contain the dehydrating agent D. The partition member 52 has a central opening or duct 53 formed therein. On top of the partition member 52, there is placed a thin layer of fine glass wool 54 which acts as a filter. On top of this layer of glass wool, within the tube 50, there is mounted a cup-shaped member 55. This is adapted to hold the powdered therapeutic agent P. There are several equi-spaced holes 56 drilled longitudinally in the sidewall of the cup-shaped member 55 from the bottom of the cup-shaped member upwardly for the greater portion of the height thereof. These holes or ducts 56 communicate with short, helically arranged ducts 57, which lead into the interior of the cup. There is a gasket 58 placed on top of the cup 55, and the cup is secured in the tube 50 by the upper cap member 60 which threads into the tube 50. The cap member 60 has a central opening therein, and in this there is mounted a short tube or duct 61. The bottoms of the cap member 60 and of the tube 61 are made to spherical shape, as denoted at 62, so as to provide a dome-like or spherical top for the chamber in which the powder P is contained.

There is a right angular duct 65 drilled or otherwise formed in the bottom end cap 51, and there is a short tube 66 mounted at one side in this end cap to communicate with the duct 65. An air pressure bulb 67, having an engaging portion 68 may be secured to the tube 66, by pushing the portion 68 over the outside of the tube 66.

To use the apparatus of Fig. 6, the patient alternately squeezes then releases the bulb 67, this forces air through the tube 66, and duct 65

into the lower chamber containing the dehydrating substance D. The dehydrating substance removes the moisture from the air. The dried air passes out of the lower chamber through the duct 53 in the partition member 52, and through the filter 54 into the ducts 56 formed in the cup-shaped member 55. Thence it flows through the ducts 57 into the interior of this cup. The helical inclination of the ducts 57 causes air flowing into the upper chamber to create a turbulence and force the powder into a spiral path. The spherical dome 62 of the upper chamber helps keep the powder agitated. From the upper chamber the air-borne powder is forced upwardly through the opening in the tube 61 to the outer air where it emits in the form of smoke.

The upper chamber of the apparatus is of reduced area because of the use of the cup 55. The small surface area increases the emptying efficiency of the powder chamber. The outlet tube 61 is likewise made of small internal calibre to reduce the amount of precipitate on the walls of the tube. The threaded connection of the upper end cap 60 with the tube 50 prevents the powder from seeping out between the tube 50 and the end cap, the thread serving, therefore, as a seal.

The apparatus shown in Fig. 6 is adapted to all the various uses of the apparatus shown in Figs. 1 to 5 inclusive. On removing the bulb 67, the outlet tube 61 can be placed in the mouth, and the powder drawn directly into the oral cavity. The outlet tube 61 can also be connected to a face mask, in a manner similar to the connection between the outlet tube 20 of Fig. 3 and the face mask of that figure, or, if desired, the outlet tube 61 can be replaced by a right angular tube for this purpose. The bulb 67 can be replaced by a pressure cuff, such as shown in Figs. 4 and 5. Various adapters can also be fitted to the outlet tube, for nasal, oral, dental, vaginal use, etc., if desired.

In some cases it may be desirable to provide an inhaler which contains a single dose of the therapeutic agent, which is to be administered, and which is disposable after use. Such an inhaler is shown in Fig. 7. This comprises a cylindrical-shaped cup or barrel 70, and a cap 71.

The cup or barrel is hollowed out to receive a measured dose of the therapeutic powder P. Ducts 72 are formed in the sidewall of the cup or barrel from the bottom 73 thereof to a point above the level of the powder P in the container. These ducts 72 communicate with helical ducts 74 that lead into the interior of the container above the level of the powder.

The cap 71, which tapers externally upwardly, has a single axial duct 75 formed therein.

The barrel and cap may be made of papier-mâché or of a suitable plastic. The measured dose is placed in the container and the cap sealed thereon. Then container and cap are dipped in some suitable sealing material or wrapped in a suitable cellulose cover so as to completely seal and cover the whole container. This sealing covering is designated at 76 in Fig. 7. Strings or wires 77 and 78 may be embedded in this covering so that when they are pulled, the part of the covering, which covers the outside end of duct 75, and the part of the covering, which covers the bottom or outside ends of ducts 72, are removed. Then the inhaler is ready for use.

In use, the patient simply puts the small end of the cap 71 into a nostril or into his mouth and inhales. Air is drawn through the ducts 72 and 74 into the powder chamber; the helical shape of the ducts creates a turbulence in the powder; and the powder in suspension is drawn up through the duct 75 into the nostril or mouth.

The principle of administering soluble, absorbable therapeutic agents in a micro-pulverized state, suspended in air with or without a vehicle, by inhallation is a new method of therapeutics. It may be applied to penicillin in the crystalline or amorphous state. It may be used as already indicated for the administration of any other absorbable therapeutic agent such as streptomycin and the sulfonamides, either separately or in combination. All of the antibiotic agents such as the sulfonamides, and streptomycin are now available in crstalline form; and in the crystalline state they are stable so long as they are kept in moisture-free containers. In addition, the invention may be used for the administration of insulin and other hormones, such as estrone, progesterone, testosterone, desoxycorticosterone, or for the administration of any of the antihistamine group of drugs in the treatment of hay fever, hives, etc., or in the administration of pituitrin, or of the vasoconstrictors, such as "Neosynephrine," "Tuamine," adrenalin, ephedrin, "Privine," "Paredrine," etc., or it may be used in the application of heparin. In case of administration of drugs of the antihistamine group, the present invention is much more effective than previous methods of treating hay fever and other allergies through hypodermic injections. With the method of the present invention the therapeutic agent is supplied directly to the nose and lungs, and does not have to be absorbed into the blood stream to begin to work.

The above named drugs can be given individually or in combination as indicated, and may be combined in a vehicle which will allow either rapid or slow absorption as desired. The drugs furthermore, may be combined with the vehicle either physically or chemically, and many combinations may be devised to fit particular needs.

The equipment and therapeutic agent may also be used for topical administration, such as for dusting open wounds, burns, otitis externa, abdominal wounds, vaginal and rectal infections, surgical wounds, etc.; and the use of the method and apparatus is not limited to inhalation procedures alone. Heretofore, for instance, in administering penicillin, streptomycin, tyrothricin, and similar substances to open wounds, they have simply been thrown into the wound. With the apparatus and method of present invention, the substance can be applied more thoroughly to the wound or burn, and more efficiently. The smoke penetrates to every part of the area to be treated and is much more effective than merely scattering the therapeutic agent over the surface.

There are certain diseases in the treatment of which this new method of therapy is particularly advantageous. In principle, they are the diseases where a high concentration of therapeutic agent at the surface of the infection or reacting organ is of special importance. Thus, the present method of therapy may be used in the treatment of diseases of the respiratory tract caused by organisms sensitive to the available antibiotics including such diseases as: tonsillitis, Vincent's angina, infected tooth sockets, diphtheria, otitis media, sinusitis, laryngitis, tracheitis, bronchitis, pneumonia, bronchiectasis, and tuberculosis. Moreover, the invention is applicable in cases of disease carriers, particularly in such cases as meningococcus, streptococcus, diphtheria, and pneumococcus. It may be used,

also, in the treatment of urinary infection particularly by use of streptomycin.

In addition, the principle of treatment involved in this invention provides a means of administration of various therapeutic agents that can be used on ambulatory patients for the venereal diseases such as gonorrhea, syphilis, chancroid, and lymphagranuloma. It can also be used for treatment of rheumatic fever. In this last-named case, sulfonamides or penicillin may be continuously administered for treatment of hemolytic streptococcal infections. The invention may be employed, also, in the treatment of meningitis, scarlet fever, pneumonia, diphtheria and streptococcal diseases in hospitals, barracks, and closely-knit communities; and for the prevention of post-operative pulmonary infections by pre-operative sterilization of the respiratory tract by use of the various antibiotics singly or in combination as indicated by the bacterial flora present.

This invention provides a new principle of therapeutics through which numerous specific drugs may be administered in micro-pulverized state, suspended in air, with or without a vehicle. The apparatus constructed according to the invention is simple to operate, inexpensive, efficient, fool-proof, and measured doses of various therapeutic agents may be administered by it in the hospital or at home in a period of two to five minutes without any of the disadvantages of the previous method of administration of such substances.

While the invention has been described in connection with particular embodiments and particular uses thereof, it will be understood that it is capable of various further modifications and uses, and that this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice in the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth and as fall within the scope of the invention or the limits of the appended claims.

Having thus described our invention, what we claim is:

1. A therapeutic agent for direct administration to humans by inhalation comprising dry, micropulverized, powdered penicillin having a particulate size in the order of one micron.

2. A therapeutic agent for direct administration to humans by inhalation comprising a dry, micropulverized, powdered, soluble antibiotic substance, from the group consisting of penicillin and streptomycin which are produced by micro-organisms, the particulate size of the micropulverized substance being in the order of one micron.

3. A therapeutic agent for direct administration to humans by inhalation comprising dry, micro-pulverized, powdered streptomycin having a particulate size in the order of one micron.

4. A therapeutic agent for direct administration to humans by inhalation comprising dry, micropulverized, powdered crystals of a soluble antibiotic substance, from the group consisting of penicillin and streptomycin which are produced by micro-organisms, the particulate size of the micropulverized crystals not exceeding one micron.

5. A therapeutic agent for direct administration to humans by inhalation comprising a dry, micropulverized, powdered mixture of glucose and a soluble antibiotic substance from the group consisting of penicillin and streptomycin which are produced by micro-organisms, the particulate size of said mixture being in the order of one micron.

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